

Development of taste-masked solid dispersion of Tizanidine hydrochloride by the salting-out solvent evaporation technique and *in vivo* taste evaluation

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The aim of this investigation was to find a way to mask the bitter taste of Tizanidine hydrochloride (TH), a centrally acting α_2 -adrenergic agonist. Solid dispersions (S1–S8) were prepared using different ratios of methyl cellulose (MC):d-sorbitol by the salting-out solvent evaporation technique. S8 containing MC:d-sorbitol 2:3 and TH 5% w/w of MC released $4.35 \pm 0.16\%$ of drug in simulated salivary fluid (SSF) after 120 seconds ($<$ threshold bitterness concentration, i.e. $20 \mu\text{g/mL}$). It was then formulated into rapid disintegrating tablets (RDTs) using diluents Avicel PH 105, spray-dried mannitol and dextrate, and superdisintegrant croscopollose. F4 containing Avicel PH 105 and spray-dried mannitol in a 1:1 ratio gave rapid disintegration (25 ± 3 seconds), a pleasant taste, a smooth feeling and rapid drug release in acid buffer pH 1.2 ($95.26 \pm 0.64\%$ in 15 minutes). Salting-out and subsequent hydrophobic chain interaction in MC molecules during formation of solid dispersion caused by sorbitol prevented MC from dissolving rapidly in SSF and masked the taste of TH.

Keywords: Methyl cellulose, d-sorbitol, taste masking, rapid disintegrating tablet.

Introduction

Bitter-tasting drugs are difficult and unpleasant for patients to swallow, leading to poor adherence and decreased therapeutic efficacy. The taste of oral medicine is one of the most vital factors affecting this adherence¹. As scores of active pharmaceutical ingredients exhibit an unpleasant taste, taste-masking becomes essentially important. Taste is largely perceived due to the interaction of dissolved molecules with different receptors located within the gustatory cells on the tongue. The mechanisms of signal transduction after binding of the substance can be different depending on the taste of the substance².

There are a variety of techniques available to mask the bitter taste of drugs, such as coating or encapsulation; chemical derivatisation to alter drug solubility; complexation with ion-exchange resins; solid dispersion; and by using sweeteners and flavours, or bitter taste blocker substances.

Coating is the most frequently employed technique for taste masking. Hydrophobic polymers, lipids or hydrophilic polymers are either used alone or in combination as coating materials. Taste masked famotidine was formulated by using

a combination of water-soluble polymer like polyvinylpyrrolidone and insoluble polymer like cellulose acetate as the coating material³. Ibuprofen was taste masked by using a combination of hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose as coating material⁴. Cetirizine was coated by fluidised bed coating using Eudragit® RL30-D to mask its bitter taste⁵.

Complexation with ion exchange resin⁶ and cyclodextrin (CD)⁷ has also been used to mask unpleasant tastes. Taste masking of famotidine was achieved by ternary complexation approach using drug, β -CD and a hydrophilic polymer HPMC⁸.

Solid dispersions using hydrophobic polymers and long-chain fatty acids have been used to accomplish taste masking of drugs. Shah and Mashru⁹ masked the intensely bitter taste of artemether by solid dispersion with monoamino glycyrrhizinate. Solid dispersions should prevent drug release in saliva in order to preclude taste perception, but it is desirable to have rapid drug release as soon as the drug reaches the gastrointestinal tract because low dissolution can cause low bioavailability. However, solid dispersions with hydrophobic polymer leads to a slow release of the drugs within the stomach. Morita¹⁰ reported that a large portion of multiparticulate dosage forms reach the stomach quickly after administration but a small portion remains in the

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epiglottic vallecula or adheres to the epiglottis and it takes 1–2 minutes for that portion to be carried to the stomach with the saliva^{11,12}. Therefore, a lag time for drug release in simulated salivary fluid (SSF) of 2 minutes is essential in order to prevent the perception of bad taste of a drug incorporated in a multiparticulate dosage form. Yoshida *et al*¹³ utilised salting-out effects of electrolytes on HPMC for developing a multiparticulate system capable of generating lag time followed by immediate release of the drug in the gastrointestinal tract. The system consisted of a salting-out layer comprising of Na₂CO₃ and HPMC over the drug core followed by an outer water penetration control layer of cetanol. The technique however was time consuming and tedious as it involved multiple coating.

Granulation/solid dispersions are rather less expensive, and an easily scalable taste masking technology. The aim of the present study was to develop a cheap and readily scalable technique for bitter tasting drug using the salting-out principle. To accomplish the objective, an attempt has been made to prepare a solid dispersion with methyl cellulose (MC) by utilising the salting-out solvent evaporation technique. Salting-out of MC was achieved using d-sorbitol which itself is widely used as a taste masking agent in oral formulations to mask bitter taste. D-sorbitol is known to decrease the gelation temperature of aqueous MC solution and cause precipitation as a consequence of its salting-out property¹⁴.

Tizanidine hydrochloride (TH) was used as the model drug due to its bitter taste. TH is a centrally acting α_2 -adrenergic agonist. It is a short-acting drug used to treat muscle spasms, cramping and tightness caused by medical conditions, such as multiple sclerosis and spastic diplegia¹⁵. For certain patient groups, administration of a conventional tablet with water two to three times a day is hard due to difficulties with swallowing. Furthermore, in cases of physical therapy or certain injuries to the spine, rapid action is desired. For such conditions, rapid disintegrating tablets (RDTs) are beneficial. Hence, a taste-masked solid dispersion of TH was subsequently formulated into RDTs.

Materials and methods

TH was gifted by Blue Cross Pharmaceutical Pvt. Ltd., Nashik, India, and MC (4000 cps) and d-sorbitol were purchased from Loba Chem Pvt. Ltd, Mumbai, India. The diluents were spray-dried mannitol (Parateck M 200, Merck, Darmstadt, Germany), Avicel PH 105 (FMC Corporation, Philadelphia, PN, USA), and dextrate (JRS Pharma GmbH, Rosenberg, Germany). The superdisintegrant was croscopolidone (Polyplasdone XL-10, ISP Technologies, Inc., Calvert City, KY, USA). All other chemicals used were of analytical grade.

Determination of threshold bitterness concentration of TH

The threshold bitterness concentration of TH was determined on the basis of bitter taste recognised by six volunteers from whom informed consent was first obtained. The protocol was approved by the Investigational Review Board. Standard aqueous solution (1 mL) with concentrations ranging from 10–100 μ g/mL was placed on the centre of the tongue for 60 seconds, and then the mouth was thoroughly rinsed with distilled water. The minimum concentration at which at least half of the volunteers perceived bitter taste was considered threshold bitterness concentration¹⁶.

Preparation of solid dispersion by salting-out solvent evaporation technique

MC at 15/20% w/v was dispersed in water and kept overnight for complete hydration. After complete hydration, drug was dissolved in the MC solution. The solution was then placed in a porcelain dish into which d-sorbitol solution with concentration 20/30% w/v was added whilst stirring. Addition of sorbitol resulted in the precipitation of MC. Water was evaporated whilst stirring at $50 \pm 2^\circ\text{C}$. Solid dispersions were dried in a hot air oven at $50 \pm 2^\circ\text{C}$ and passed through a number 40 sieve. Batches S1–S8 were prepared using different ratios of MC:d-sorbitol and drug at the concentration level 10/5 w/w of MC (Table 1).

Table 1. Composition of the solid dispersions.

Solution number	Formulation	Ingredient		
		MC % w/v	D-sorbitol % w/v	Drug (% w/w of MC)
1	S1	15	20	10
2	S2	15	30	10
3	S3	20	20	10
4	S4	20	30	10
5	S5	15	20	5
6	S6	15	30	5
7	S7	20	20	5
8	S8	20	30	5

Table 2. Drug content and *in vitro* taste evaluation of solid dispersion in SSF.

Solution number	Batch	Amount of TH (mg)/100 mg of solid dispersion*	Concentration of drug in SSF ($\mu\text{g/mL}$) after 120 seconds*	% Drug dissolved in SSF after 120 seconds*
1	S1	4.13 ± 0.41	34.70 ± 0.45	8.61 ± 0.11
2	S2	3.15 ± 0.32	32.0 ± 0.40	7.94 ± 0.10
3	S3	4.60 ± 0.36	29.10 ± 0.26	7.19 ± 0.02
4	S4	3.87 ± 0.17	25.16 ± 0.37	6.24 ± 0.09
5	S5	2.10 ± 0.17	24.50 ± 0.52	6.08 ± 0.13
6	S6	1.83 ± 0.09	23.43 ± 0.92	5.81 ± 0.22
7	S7	2.43 ± 0.04	22.63 ± 0.55	5.61 ± 0.13
8	S8	1.96 ± 0.02	17.53 ± 0.65	4.35 ± 0.16

* Results are the mean of three observations $\pm$ SD.

Evaluation of solid dispersion

Determination of drug content

Solid dispersion (100 mg) was dissolved in 100 mL of acid buffer pH 1.2. After suitable dilution, drug content was estimated UV-spectrophotometrically at 320 nm using acid buffer at pH 1.2 as a blank (Table 2).

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of TH, MC, the physical mixture of TH and MC, and the solid dispersion were obtained by KBr disc method (8400 S, Shimadzu Asia Pacific Pvt. Ltd, Singapore) in the range of 4000 to 500 cm^{-1} (Figure 1).

Differential scanning calorimetry (DSC)

DSC analysis of TH, MC, d-sorbitol, the physical mixture of TH, MC and d-sorbitol, and the solid dispersion was performed using DSC equipped with computer

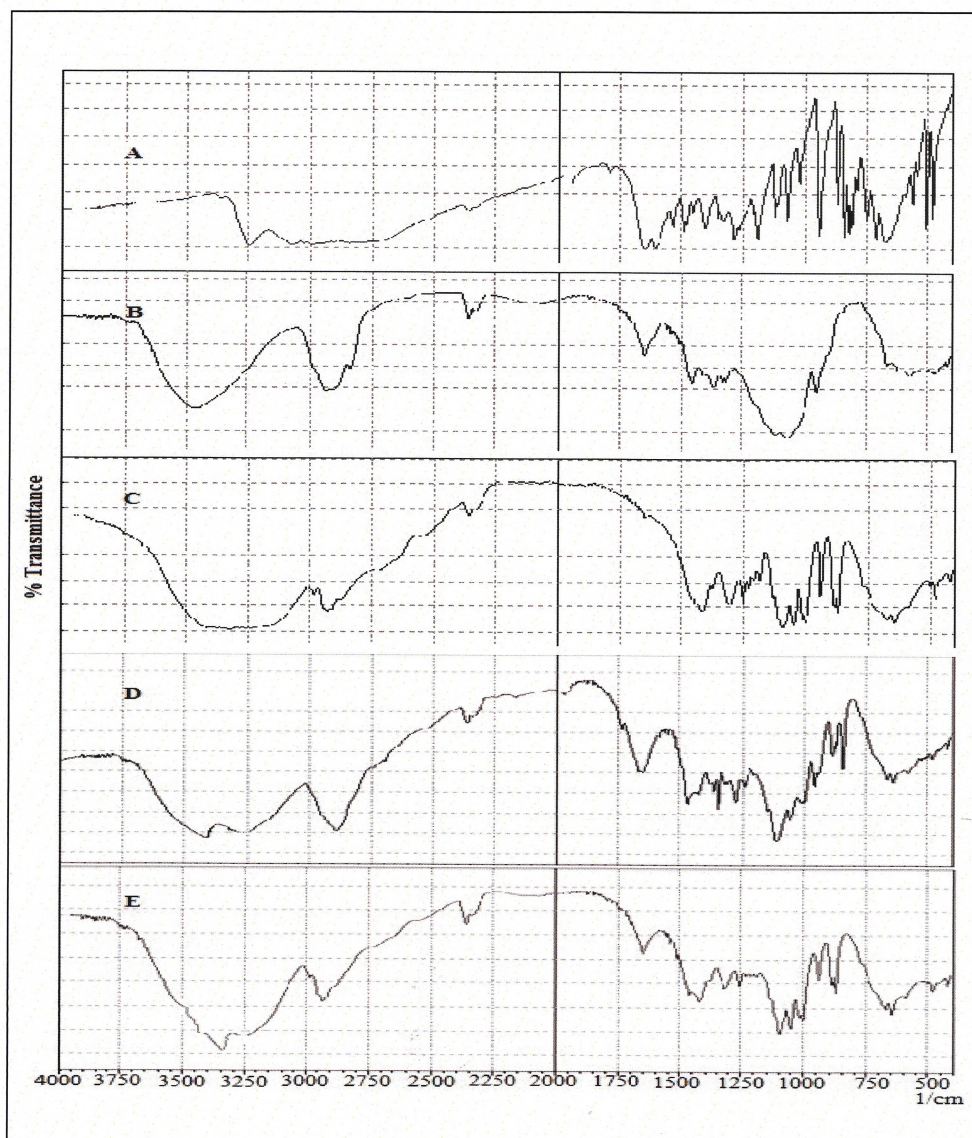


Figure 1. FTIR spectra of (A) TH; (B) MC; (C) d-sorbitol; (D) physical mixture of TH, MC and d-sorbitol; (E) solid dispersion.

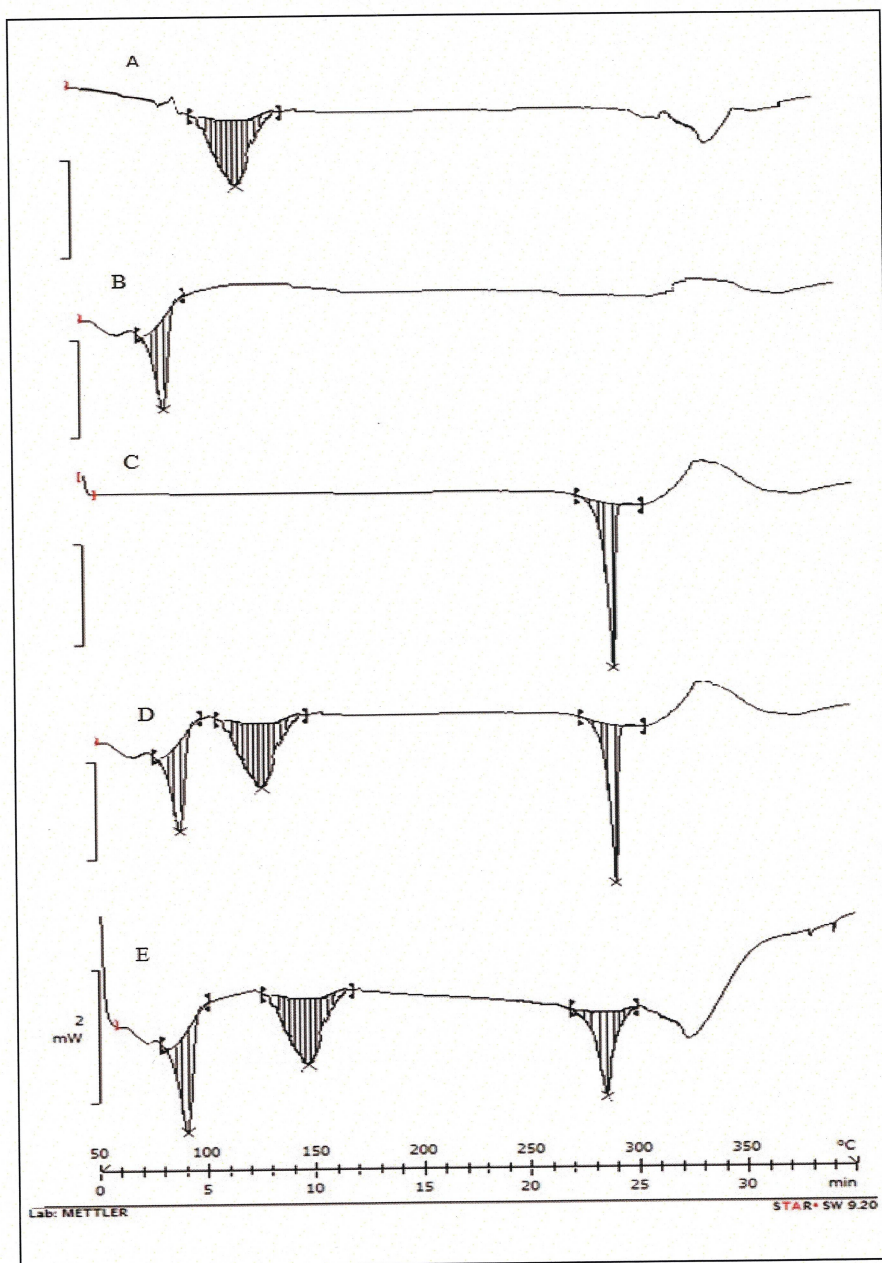


Figure 2. DSC thermograms of (A) MC; (B) d-sorbitol; (C) TH; (D) physical mixture of d-sorbitol, MC and TH; E) solid dispersion.

analyser (DSC Mettler Toledo DSC 821, Japan). Samples (4–6 mg) were heated under nitrogen atmosphere on an aluminium pan at a heating rate of 10°C/minute over the temperature range of 50–350°C (Figure 2).

Drug release study in SSF

Drug release from the solid dispersion was studied in SSF at pH 6.2 for approximation of drug release in the human saliva before performing the volunteer study for taste. As it takes 2 minutes to pass over the epiglottis^{11,12}, drug release in SSF was observed for 2 minutes. Drug release less than the bitter threshold concentration in 2 minutes was considered the lag time. A solid dispersion equivalent to 4 mg of TH was taken in a 25 mL volumetric flask. To this, 10 mL of SSF was added and shaken for 120 seconds¹⁷. A 0.5 mL aliquot of the sample was withdrawn and diluted suitably with SSF. The amount of drug released was analysed spectrophotometrically at 320 nm (Table 2).

Formulation of RDTs

All the ingredients were weighed, mixed and compressed into tablet form using an 8 mm flat-faced punch on a single tablet punching machine under the compressional force of 8 KN. Composition of the TH RDT by the direct compression method is shown in Table 3. Flow properties and compression

Table 3. Composition of RDTs.

Ingredients (mg)	Batch					
	F1	F2	F3	F4	F5	F6
Solid dispersion, S8 (equivalent to 4 mg TH)	204	204	204	204	204	204
Avicel PH 105	180	–	–	90	90	–
Spray-dried mannitol (Parateck)	–	180	–	90	–	90
Dextrate (Emdex)	–	–	180	–	90	90
Crosspovidone	30	30	30	30	30	30
Magnesium stearate	6	6	6	6	6	6

Table 4. Flow properties and compression parameters of tablet blends.

Parameter	F1	F2	F3	F4	F5	F6
Bulk density (g/cc)*	0.35 ± 0.07	0.58 ± 0.05	0.71 ± 0.07	0.47 ± 0.13	0.61 ± 0.07	0.65 ± 0.14
Tapped density (g/cc)*	0.48 ± 0.06	0.74 ± 0.08	0.81 ± 0.06	0.61 ± 0.12	0.77 ± 0.08	0.77 ± 0.09
Angle of repose (°)*	56.0 ± 5.58	35.30 ± 4.50	30.0 ± 5.20	40.0 ± 4.35	36.30 ± 5.13	32.0 ± 4.58
Compressibility (%)*	27.80 ± 24.9	21.50 ± 1.59	12.77 ± 3.81	23.73 ± 6.98	21.06 ± 3.66	16.9 ± 9.26
Hausner ratio*	1.36 ± 0.09	1.27 ± 0.02	1.14 ± 0.04	1.31 ± 0.11	1.26 ± 0.05	1.21 ± 0.14

* Results are the mean of three observation ± SD.

Table 5. Evaluation of tablets.

Parameter	F1	F2	F3	F4	F5	F6
Hardness (kg)*	4.83 ± 0.28	6.73 ± 0.68	7.90 ± 0.36	5.96 ± 0.87	6.36 ± 0.76	7.30 ± 0.75
Friability (%)*	0.45 ± 0.05	0.40 ± 0.02	0.32 ± 0.06	0.37 ± 0.05	0.38 ± 0.06	0.34 ± 0.05
Content uniformity (%)*	99.30 ± 0.30	99.90 ± 0.36	99.40 ± 0.40	99.50 ± 0.40	98.90 ± 0.26	99.20 ± 0.60
Disintegration time (S)*	22.30 ± 2.50	42.0 ± 3.6	54.30 ± 3.20	25.0 ± 3.0	36.0 ± 4.0	50.30 ± 3.50

* Results are the mean of three observation ± SD.

Table 6. *In vivo* taste and sensory evaluation.

Formulation	Degree of bitterness after time*						Degree of roughness†
	10 seconds	1 minute	2 minutes	5 minutes	10 minutes	15 minutes	
Pure TH	0.5	2.0	2.5	3.0	3.0	3.0	NA
Solid dispersion	0	0.1	0.2	0.3	0	0	NA
F1	0	0	0.1	0.2	0	0	0.3
F2	0	0	0	0	0	0	0
F3	0	0	0	0	0	0	0
F4	0	0	0.1	0.1	0	0	0
F5	0	0	0.1	0.1	0	0	0
F6	0	0	0	0	0	0	0

* Results are the mean of eleven observations; † Results are the mean of six observations; NA: not applicable.

parameters of the tablet blend (Table 4) and the physical properties of the tablets were determined (Table 5).

Evaluation of RDTs

Drug content

Ten tablets were taken and triturated in a glass mortar. The powdered tablet equivalent to 4 mg of solid dispersion of drug was dissolved in a 100 mL acid buffer at pH 1.2 and the drug content was determined spectrophotometrically at 320 nm (Table 5).

In vitro disintegration

In vitro disintegration time of the RDTs was determined using a modified disintegration apparatus designed by Khan *et al*¹⁷. Briefly, the apparatus consisted of a glass beaker (1000 mL) with the wire basket positioned in the beaker with the aid of a support in a way that when the beaker contained 900 mL of disintegrating medium (SSF pH 6.2), the basket had only 6 mL of it. A magnetic bead was placed at the bottom of the beaker maintained at 37 ± 2°C and a tablet was placed in the basket. Disintegration time was determined at 25 rpm (Table 5).

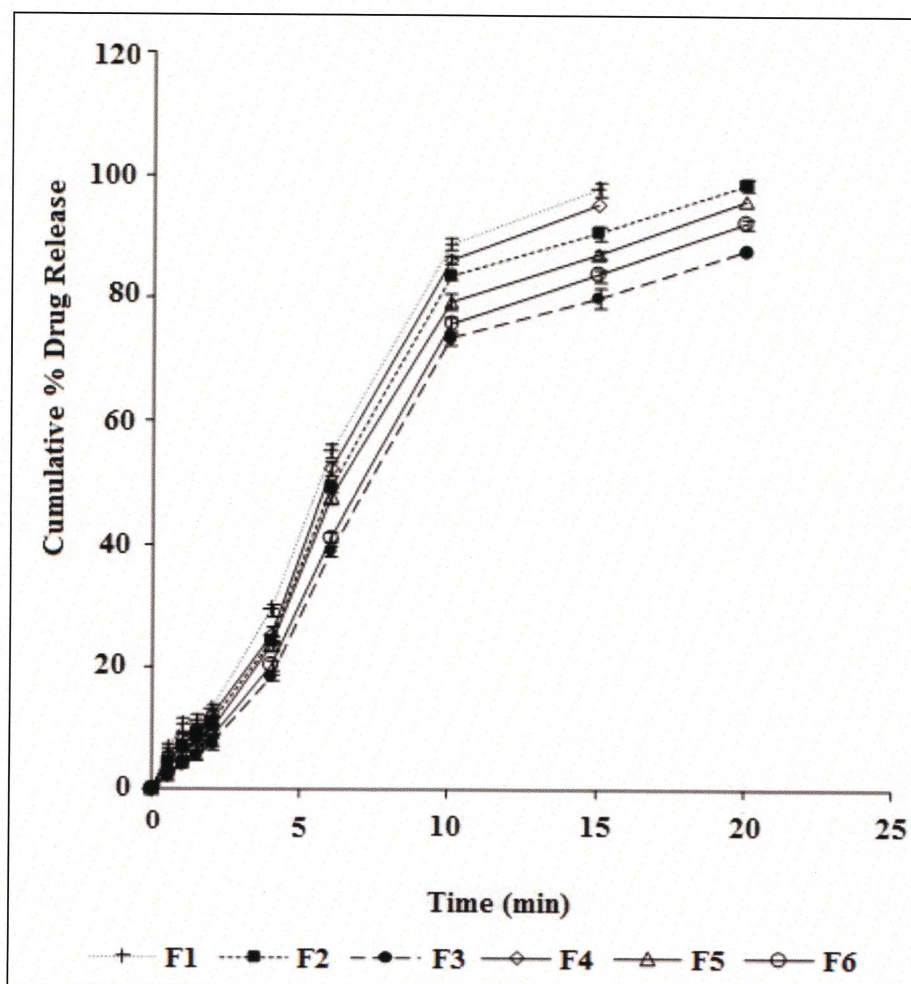


Figure 3. *In vitro* drug release of RDTs.

In vivo taste evaluation and sensory evaluation of roughness

Taste evaluation was performed using time intensity method on 11 healthy human volunteers from whom informed consent was obtained. The protocol was approved by the Investigational Review Board. Solid dispersion equivalent to 4 mg of TH was held in the mouth for 10 seconds and then spat out and then one RDT (containing 4 mg TH) was held in the mouth until completely disintegrated. Bitterness perception was recorded immediately and at several time points for a total of 15 minutes according to the bitterness intensity scale from 0 to 3, where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness, respectively. After the study, the mouth was rinsed with water¹⁸. The results are shown in Table 6.

Sensory evaluation was completed on six volunteers from whom informed consent was obtained. One tablet was held in the mouth and allowed to disintegrate. The disintegrated material was retained for 60 seconds and then spat out. The mouth was rinsed with water without swallowing the disintegrated material and finally the roughness levels were scored as 0, 1 and 2 indicating not rough, slightly rough and markedly rough, respectively¹⁹ (Table 6).

In vitro dissolution study in acid buffer pH 1.2

In vitro dissolution testing of RDTs of different batches was performed using USP type II (paddle) dissolution apparatus at 50 rpm and 500 mL acid buffer at pH 1.2 as the dissolution medium. The temperature of the medium was maintained at $37 \pm 0.5^\circ\text{C}$. Aliquots (5 mL) of the dissolution medium were withdrawn at specific time intervals, diluted suitably and analysed by a UV-visible spectrophotometer at 320 nm, and the cumulative percentage drug release was determined (Figure 3).

Results and discussion

Threshold bitterness concentration of TH and drug content in solid dispersion

The threshold bitterness concentration of TH was found to be $20 \mu\text{g/mL}$. The drug content of solid dispersion ranged from 1.83 ± 0.88 to 4.71 ± 0.34 mg TH per 100 mg solid dispersion for batches S1–S8. The drug content decreased with increasing polymer concentration.

FTIR spectroscopy

FTIR of TH shows peaks at 3244.05 cm^{-1} , 3072.39 cm^{-1} and 1643.24 cm^{-1} due to secondary NH stretching, C-H stretching and C=N stretching, respectively. The characteristic peaks of TH at 3244.05 cm^{-1} , 3072.39 cm^{-1} and 1643.24 cm^{-1} were retained in the physical mixture of drug, MC and d-sorbitol confirming no drug–excipient interaction. The broad peak between $3600\text{--}3100 \text{ cm}^{-1}$ in the FTIR of solid dispersion is attributed to the OH group, which may be due to the formation of an intermolecular H-bond between the NH group of TH and the OH group of d-sorbitol.

DSC

DSC of TH showed a sharp endothermic peak at 290°C while d-sorbitol and MC showed melting endothermic peaks at 90°C and 130°C , respectively. DSC of the physical mixture of MC, d-sorbitol and TH showed retention of the melting peak at 290°C of TH. The sharp endothermic peak at 290°C in the DSC of TH is attributed to the melting of the drug whilst the appearance of an additional endothermic peak in the DSC of the physical

mixture of MC and TH near 120°C is due to dehydration of MC. In the solid dispersion, the melting peak of MC had shifted to 148°C. Shifting of the melting peak of MC to 148°C in the solid dispersion might be due to greater intermolecular interaction between MC molecules as a consequence of the salting-out effect of d-sorbitol followed by precipitation of MC during formation of the solid dispersion. Thus, more energy was required to break them apart.

The melting endotherm of TH had shifted to 283°C (Figure 2) and was also found broadened in the solid dispersion. The decrease in melting temperature and broadening of the peak of TH in the DSC of the solid dispersion might be due to the decrease in crystallinity of the drug after dispersion.

In vitro taste evaluation

Percentage drug release from solid dispersions S1–S8 in pH 6.2 SSF after 120 seconds was found between $8.61 \pm 0.11\%$ to $4.35 \pm 0.16\%$. Solid dispersions S4 and S8 containing 30% w/v d-sorbitol gave $6.24 \pm 0.09\%$ and $4.35 \pm 0.16\%$ drug release, respectively, in simulated SSF at pH 6.2 in 120 seconds. The percentage drug release from S8 corresponds to the mean concentration $17.53 \pm 0.65 \mu\text{g/mL}$ which is less than the threshold bitterness concentration ($20 \mu\text{g/mL}$).

Sorbitol, which is responsible for salting-out and precipitation of MC during the formation of the solid dispersion of TH prevented MC from dissolving in SSF, which is a fairly water-soluble polymer. The slow dissolution of MC suppressed drug release in SSF¹³. Sorbitol (a polyol), owing to its high water solubility²⁰, competes for water and dissolves first, causing slower dissolution of MC, which consequently retarded the drug release in SSF. With the rise in percentage of sorbitol in the dispersion, drug release was decreased. Solid dispersions S4 and S8 had the same level of sorbitol, but drug release from S8 was less as it had a lower percentage of drug.

Flow properties and compression behaviour of tablet blend

Tablet blend F1 (with Avicel PH 105 as the filler) had the lowest bulk density and very poor flow property (angle of repose $56 \pm 5.58^\circ$). High percentage compressibility ($27.82 \pm 4.9\%$) and Hausner ratio (1.36 ± 0.09) also demonstrated poor flow character of blend F1. F1 showed very poor flow behaviour because it consisted of only Avicel PH 105 as the filler. Avicel PH 105 possesses low bulk density and very small particle size ($20 \mu\text{m}$) and therefore its flow property is poor. When Avicel PH 105 was replaced with spray-dried mannitol in blend F2, flow property improved. The angle of repose of blend F2 was $35.3 \pm 4.5^\circ$ while compressibility index and Hausner ratio were $21.5 \pm 1.59\%$ and 1.27 ± 0.02 , respectively.

Tablets with blend F3 which had dextrate as the filler had the highest bulk density ($0.71 \pm 0.07 \text{ g/cc}$) and showed excellent flow behaviour (angle of repose $30 \pm 5.2^\circ$, compressibility index $12.77 \pm 3.81\%$ and Hausner ratio 1.14 ± 0.04). The addition of spray-dried mannitol or

dextrate to Avicel PH 105 in a 1:1 ratio as the filler improved flow behaviour of the tablet blends, because spray-dried mannitol has a free-flowing granular characteristic²¹, and dextrate is composed of porous spheres that have excellent flow properties²². Flow behaviour of blend F4 was fair (angle of repose $40 \pm 4.35^\circ$) while it was good in blend F5 (angle of repose $36.3 \pm 5.13^\circ$).

Evaluation of RDTs

Hardness and disintegration time

Tablets containing dextrate as filler (F3) were hardest (hardness $7.9 \pm 0.36 \text{ kg}$) followed by those containing spray-dried mannitol (F2, hardness $6.73 \pm 0.68 \text{ kg}$) and Avicel PH 105 (F1, hardness $4.83 \pm 0.28 \text{ kg}$) as filler. F1, despite having Avicel alone as the filler, had good hardness because Avicel PH 105 has greatest compactibility amongst all grades of microcrystalline celluloses due to its smaller size, which increases bonding surface area. The compaction behaviour of powders depends on the deformation behaviour and their intrinsic bonding properties. Primary particles of mannitol exhibit plastic deformation and form a large surface area for bonding²¹.

Consolidation of dextrate is reported to arise by plastic deformation of the porous particles that occurs along many planes giving a large surface area for bonding²². Hence, formulations F2 and F3 containing spray-dried mannitol and dextrate produced harder tablets. Disintegration of tablet blend F1 (which contained only Avicel PH 105) was fastest (22.3 ± 2.5 seconds). Tablets with mannitol (F2) or dextrate (F3) disintegrated relatively slowly. Combination of Avicel with mannitol in the ratio 1:1 (F4) resulted in a rise in the tablet strength (hardness $5.96 \pm 0.87 \text{ kg}$), but maintained the rapid disintegrating property imparted by Avicel PH 105 (disintegration time 25 ± 3 seconds). F1 fragmented most rapidly because Avicel has the ability to promote disintegration quickly. Although the hardness of tablets increased when mannitol was added to formulations containing Avicel (F4), the rapid disintegrating property of the tablets was maintained because mannitol is less soluble when compared to other polyols and allows water penetration into the tablet²¹. Formulation F3 containing dextrate showed longer disintegration time because dextrate is highly water soluble and starts dissolving from the surface with poor penetration of water into the tablet²².

In vivo taste and sensory evaluation

TH was perceived as an intensely bitter material while the solid dispersion and RDTs were scored as non-bitter by the volunteers. The taste masking was significant with $p < 0.01$ (ANOVA followed by Dunnett test). RDTs did not give a feeling of roughness after disintegration in the mouth. Two out of six volunteers felt slight roughness with formulation F1 but others felt it smooth, therefore the average score was 0.3. The bitter taste of TH was masked in the solid dispersion because the salting-out agent, d-sorbitol, present in the solid dispersion retarded

dissolution of MC which consequently prevented drug release in the mouth. Sorbitol, being highly water soluble dissolves first preventing MC from dissolving, which consequently retarded drug release. In addition, the dissolution of sorbitol imparts sweetness and a pleasant mouth feel.

In vitro dissolution studies in acid buffer pH 1.2

All formulations showed initial slow drug release followed by rapid release in acid buffer pH 1.2. Drug release was fastest from F1 ($98 \pm 0.9\%$ in 15 minutes) which had Avicel PH 105 as the filler. Formulations which had spray-dried mannitol (F2) and dextrate (F3) as the filler showed slower drug release than F1. Formulation with dextrate (F3) gave the slowest drug release ($87.83 \pm 1.75\%$ in 20 minutes). Formulation F4 containing a combination of Avicel and spray-dried mannitol in a 1:1 ratio maintained rapid drug release ($95.26 \pm 0.64\%$ in 15 minutes). The initial slow release was due to the presence of sorbitol in the solid dispersion. As described previously, sorbitol having high affinity for water²⁰ dissolves first, retarding the dissolution of MC. Also the salting-out of MC by sorbitol during formation of the solid dispersion resulted in increased hydrophobic interaction among MC molecules, which caused poor dissolution of MC. After the sorbitol was completely dissolved, the tablet mass became porous with greater penetration of water and subsequent rapid drug release. Formulation F2 gave slower drug release than F1 because the diluent spray-dried mannitol in F2 primarily dissolves owing to its good water solubility, and reduces water penetration into the tablet, consequently leading to poor swelling of crosspovidone with subsequent delay in disintegration time. Formulation F3 gave the slowest drug release because dextrate was the diluent. Dextrate owing to its very high water solubility caused the tablet to dissolve poorly due to the very poor penetration of water, leading to the longest disintegration time²². Formulation F4, despite containing spray-dried mannitol, maintained rapid drug release because mannitol is less soluble in water compared to other polyols thus allowing water penetration into the tablet²¹. Additionally, it could be theorised that the Avicel present in the formulation promotes water penetration.

Conclusion

A taste-masked solid dispersion of TH was successfully prepared by a cost-effective, simple and scalable technique using MC and d-sorbitol. Solid dispersion formulation S8 containing MC:d-sorbitol in the ratio 2:3 with TH 5% w/w of MC released detectable TH less than the threshold bitterness concentrations in SSF. RDTs of the solid dispersion containing a combination of Avicel PH 105 and spray-dried mannitol as diluents (F4) showed good hardness, rapid disintegration, a pleasant taste, a smooth feeling and rapid drug release in acid buffer.

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